

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended): A process for constructing a signaling molecule by labeling a biological molecule, which can bind to a targeted partner, said process comprising covalently bonding to ~~a the~~ biological molecule a labeling agent, wherein said labeling agent ~~which~~ is a fluorescent conjugate comprising an oligonucleotide covalently bonded to a rare-earth metal cryptate.
2. (Previously Presented): The process as claimed in claim 1, wherein the oligonucleotide consists of a chain of ribonucleotide or deoxyribonucleotide units bonded to one another via phosphodiester bonds.
3. (Currently Amended): The process as claimed in claim 1, wherein the oligonucleotide consists of a chain of ribonucleotide or deoxyribonucleotide units or of analogous units of nucleotides modified on the sugar or on the base and bonded to one another via natural phosphodiester internucleotide bonds, wherein some of the internucleotide bonds are optionally ~~being~~ replaced with phosphonate, phosphoramidate or phosphorothioate bonds.
4. (Previously Presented): The process as claimed in claim 1, wherein the oligonucleotide consists of a chain comprising both ribonucleotide or deoxyribonucleotide units bonded to one another via phosphodiester bonds and analogous units of nucleosides bonded to one another via amide bonds.
5. (Currently Amended): The process as claimed in claim 1, wherein the oligonucleotide consists of ribonucleotide or deoxyribonucleotide units, wherein one of said units comprises ~~which may comprise~~ a functional group selected from ~~of~~ NH₂, COOH, CHO, OH, SH, halide, sulfonate, epoxide, and ~~or~~ maleimide, introduced onto or generated on said one of said

units ~~unit~~, or the functional group is introduced using a spacer arm bonded to the terminal phosphate group in the 3' or 5' position.

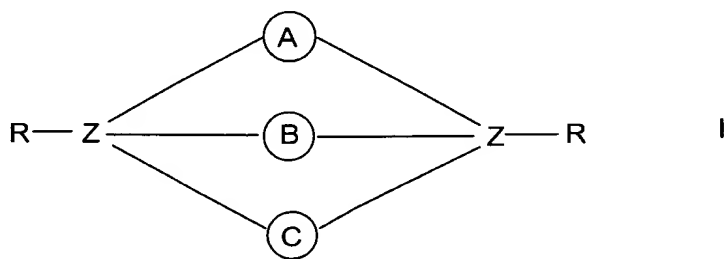
6. (Previously Presented): The process as claimed in claim 5, wherein said unit is the 5' terminal unit or 3' terminal unit.

7. (Previously Presented): The process as claimed in claim 1, wherein the oligonucleotide comprises a chain of 5 to 50 nucleotides or a chain of 5 to 50 nucleotides and nucleotide or nucleoside analogs.

8. (Currently Amended): The process as claimed in claim 1, wherein the oligonucleotide consists of a chain of ribonucleotide or deoxyribonucleotide units bonded to one another via phosphodiester bonds and of analogous units of nucleosides bonded to one another via amide bonds, said oligonucleotide comprising at least 5 phosphodiester internucleotide bonds at the end ~~intended to be~~ bonded to the cryptate.

9. (Previously Presented): The process as claimed in claim 1, wherein the rare-earth metal cryptate is bonded covalently to the oligonucleotide either directly or via a spacer arm.

10. (Currently Amended): The process as claimed in claim 1, wherein said rare-earth metal cryptate consists of at least one rare-earth metal salt complexed with a macropolycyclic compound of formula I



wherein ~~in which~~

Z is an atom with 3 or 4 valencies,

R is absence or is nothing or represents hydrogen, a hydroxy group, an amino group or a hydrocarbon-based radical, and

the divalent radicals (A) , (B) and (C) , are, independently of each other, hydrocarbon-based chains which optionally contain one or more hetero atoms and are optionally interrupted with a hetero macrocycle,

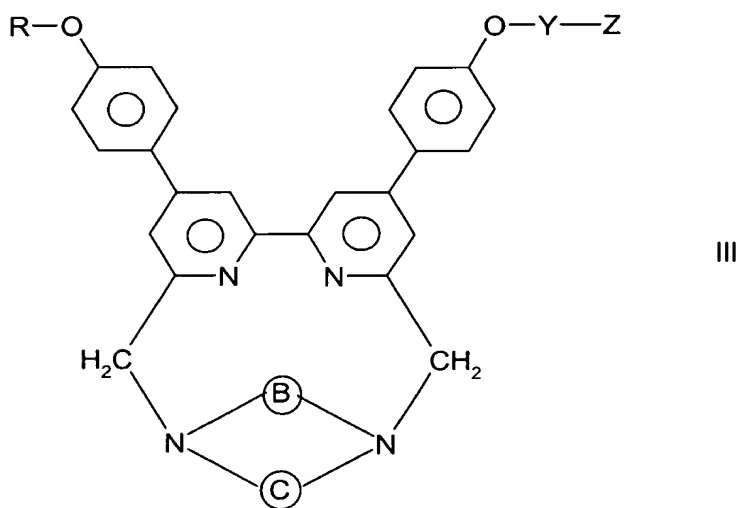
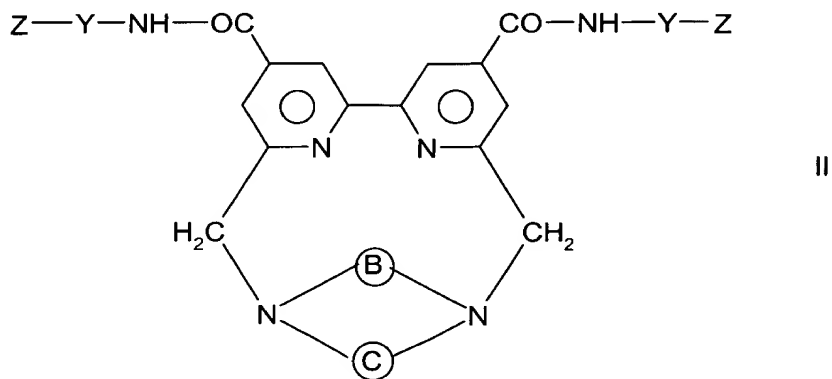
wherein at least one of the radicals (A) , (B) and (C) , also comprises ~~comprising~~ at least one molecular unit ~~or consisting essentially of a molecular unit~~, said molecular unit having a triplet energy which is greater than that of the emission level of the complexed rare-earth metal ion.

11. (Currently Amended): The process as claimed in claim 10, wherein the rare-earth metal cryptate consists of a rare-earth metal salt complexed with one of the macrocyclic or macropolycyclic compounds selected from the following compounds below:

2.2.phenanthroline, 2.2.phenanthroline amide, 2.2.anthracene, 2.2.anthracene amide, 2.2.biisoquinoline, 2.2.biphenyl-bis-pyridine, 2.2.bipyridine, 2.2.bipyridine amide, trisbipyridine, trisphenanthroline, phenanthrolinebisbipyridine, biisoquinolinebisbipyridine, bisbipyridine diphenylbipyridine, and macropolycyclic compounds comprising a molecular unit chosen from bipyrazines, bipyrimidines and nitrogen-containing heterocycles comprising N-oxide groups.

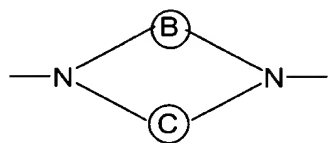
~~[2.2.phenanthroline]; [2.2.phenanthroline amide]; [2.2.anthracene]; [2.2.anthracene amide]; [2.2.biisoquinoline]; [2.2.biphenyl-bis-pyridine]; [2.2.bipyridine]; [2.2.bipyridine amide]; the macropolycycles trisbipyridine, trisphenanthroline, phenanthrolinebisbipyridine, biisoquinolinebisbipyridine, bisbipyridine diphenylbipyridine; a macropolycyclic compound comprising a molecular unit chosen from bipyrazines, bipyrimidines and nitrogen-containing heterocycles comprising N-oxide groups.~~

12. (Currently Amended): The process according to claim 1, wherein the rare-earth metal cryptate consists of at least one rare-earth metal salt complexed with a macropolycyclic compound corresponding to one of the formulae II or III below:

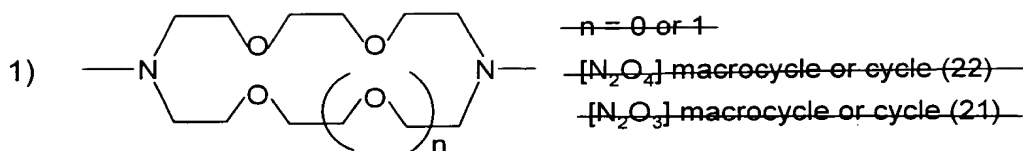


in which:

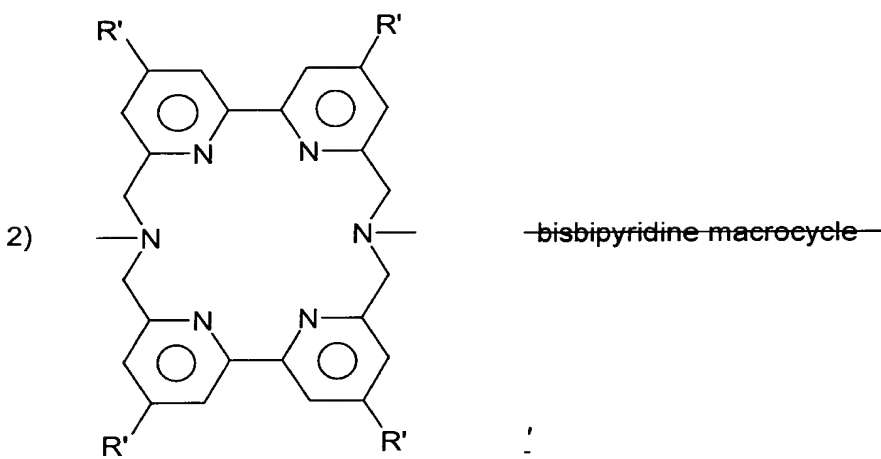
- the ring of formula



is one of the following rings:



wherein n is 0 or 1,



$[[-]]$ Y is a spacer group or spacer arm which ~~is consists of~~ a divalent organic radical $[[,]]$ chosen from:

linear or branched C_1 or C_{20} alkylene ~~groups~~ optionally containing one or more double bonds and/or optionally containing one or more hetero atoms ~~such as oxygen, nitrogen, sulfur or phosphorus~~ or one or more carbamoyl or carboxamido group(s), $[[;]]$ ~~chosen from~~

C_5 to C_8 cycloalkylene, and ~~groups or chosen from~~

C_6 to C_{14} arylene ~~groups~~,

said alkylene, cycloalkylene or arylene are in each case ~~groups being~~ optionally substituted with alkyl, aryl or sulfonate groups;

$[[-]]$ Z is a functional group capable of bonding covalently to a biological substance;

$[[-]]$ R is a methyl ~~group~~ or ~~represents the group~~ -Y-Z;

[[-]] R' is hydrogen, ~~or a group -COOR'', or -CO-NH-Y-Z; in which~~
R'' is a C₁ to C₁₀ alkyl ~~group or alternatively R' is a group -CO-NH-Y-Z.~~

13. (Currently Amended): The process as claimed in claim 1, wherein the rare-earth metal cryptate is bonded to the oligonucleotide via a spacer arm, wherein said spacer arm is consisting of a divalent organic radical chosen from:

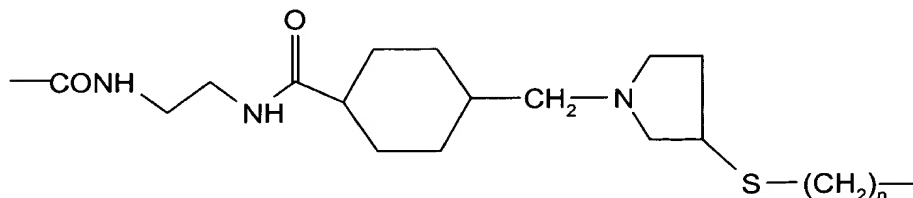
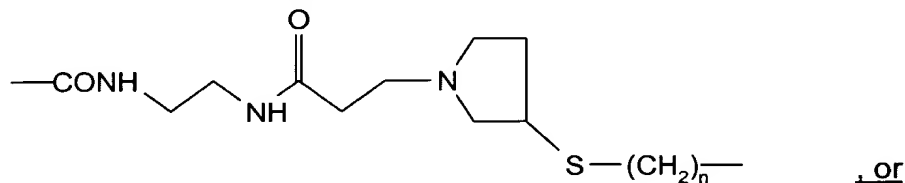
C₁-C₂₀ linear or branched alkylene ~~groups~~ optionally containing one or more double bonds or triple bonds and/or optionally containing one or more hetero atoms, ~~such as oxygen, nitrogen, sulfur, phosphorus~~ or one or more carbamoyl or carboxamino group(s);

C₅-C₈ cycloalkylene; ~~groups~~ and

C₆-C₁₄ arylene ~~groups~~; [[,]]

wherein said alkylene, cycloalkylene or arylene is in each case ~~groups being~~ optionally substituted with alkyl, aryl or sulfonate groups.

14. (Currently Amended): The process as claimed in claim 13, wherein said the spacer arm is ~~chosen from the groups:~~



wherein

n is ~~in which n =~~ 2 to 6 [[,]] ; or

the spacer arm is and -CONH-(CH₂)₆-; [[,]]

wherein the attachment to the cryptate occurs via the group -CONH taking place on the cryptate.

15. (Currently Amended): The process method as claimed in claim 1, wherein the rare-earth metal cryptate is a europium cryptate.

16. (Currently Amended): The process as claimed in claim 15, wherein ~~the rare-earth metal cryptate is the~~ said europium cryptate is Eu trisbipyridine or Eu[bisdiethoxybipyridine.bipyridine].

17. (Currently Amended): A fluorescence assay method for detecting an analyte comprising providing a measuring medium containing a sample to be tested for the presence of said analyte, wherein said measuring medium contains at least one fluorescent label, The process as claimed in claim 1, wherein said at least one fluorescent label is a the fluorescent conjugate according to claim 20 is used as the only label or as one of the fluorescent labels in the assay.

18. (Canceled)

19. (Currently Amended): The method process as claimed in claim 1, wherein said measuring medium further comprises, in addition to said fluorescent conjugate, a fluorescent label comprising an acceptor fluorescent compound in the assay.

20. (Currently Amended): A conjugate [[,]] comprising:
(1) a rare-earth metal cryptate;
(2) an oligonucleotide; and
(3) a biological molecule having a recognition role and which can bind to a partner,
wherein said cryptate, oligonucleotide, and biological molecule are (1), (2) and (3) being-linked by covalent bonds.

21. (Previously Presented): The conjugate according to claim 20, wherein the biological molecule is one member of a pair molecules capable of binding specifically to one another.

22. (Previously Presented): The conjugate as claimed in claim 20, wherein the oligonucleotide consists of a chain of ribonucleotide or deoxyribonucleotide units bonded to one another via phosphodiester bonds.

23. (Currently Amended): The conjugate as claimed in claim 20, wherein the oligonucleotide consists of a chain of ribonucleotide or deoxyribonucleotide units or of analogous units of nucleotides modified on the sugar or on the base and bonded to one another via natural phosphodiester internucleotide bonds, wherein some of the internucleotide bonds are optionally ~~being~~ replaced with phosphonate, phosphoramidate or phosphorothioate bonds.

24. (Previously Presented): The conjugate as claimed in claim 20, wherein the oligonucleotide consists of a chain comprising both ribonucleotide or deoxyribonucleotide units bonded to one another via phosphodiester bonds and analogous units of nucleosides bonded to one another via amide bonds.

25. (Currently Amended): The conjugate as claimed in claim 20, wherein the oligonucleotide consists of ribonucleotide or deoxyribonucleotide units, wherein one of said units comprises ~~which may comprise~~ a functional group selected from ~~of~~ NH₂, COOH, CHO, OH, SH, halide, sulfonate, epoxide, and ~~or~~ maleimide, introduced onto or generated on said one of said units ~~unit~~, or the functional group is introduced using a spacer arm bonded to the terminal phosphate group in the 3' or 5' position.

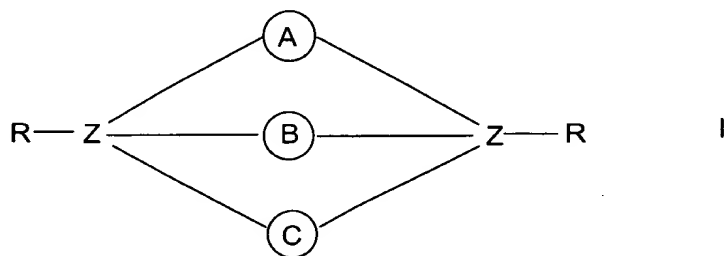
26. (Previously Presented): The conjugate as claimed in claim 25, wherein said unit is the 5' terminal unit or 3' terminal unit.

27. (Previously Presented): The conjugate as claimed in claim 20, wherein the oligonucleotide comprises a chain of 5 to 50 nucleotides or a chain of 5 to 50 nucleotides and nucleotide or nucleoside analogs.

28. (Currently Amended): The conjugate as claimed in claim 20, wherein the oligonucleotide consists of a chain of ribonucleotide or deoxyribonucleotide units bonded to one another via phosphodiester bonds and of analogous units of nucleosides bonded to one another via amide bonds, said oligonucleotide comprising at least 5 phosphodiester internucleotide bonds at the end ~~intended to be~~ bonded to the cryptate.

29. (Previously Presented): The conjugate as claimed in claim 20, wherein the rare-earth metal cryptate is bonded covalently to the oligonucleotide either directly or via a spacer arm.

30. (Currently Amended): The conjugate as claimed in claim 20, wherein said rare-earth metal cryptate consists of at least one rare-earth metal salt complexed with a macropolycyclic compound of formula I



wherein in which

Z is an atom with 3 or 4 valencies,

R is absence or is nothing or represents hydrogen, a hydroxy group, an amino group or a hydrocarbon-based radical, and

the divalent radicals (A) , (B) and (C) , are, independently of each other, hydrocarbon-based chains which optionally contain one or more hetero atoms and are optionally interrupted with a hetero macrocycle,

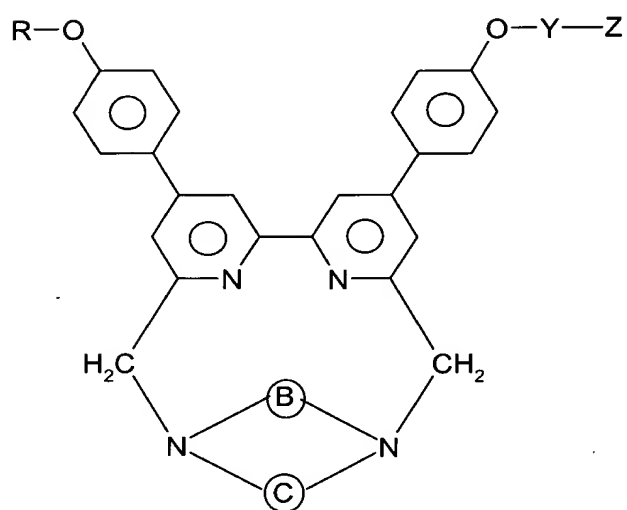
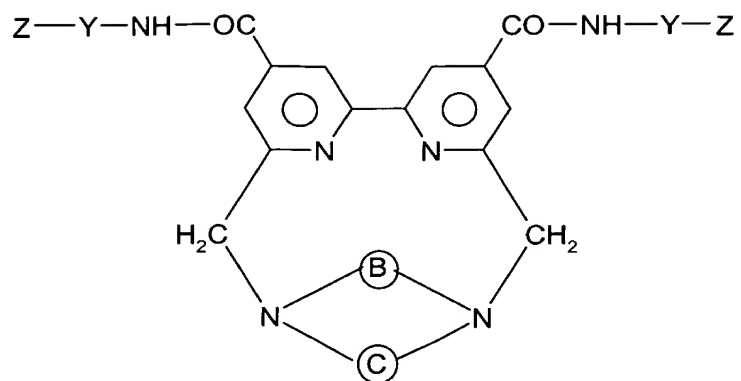
wherein at least one of the radicals (A) , (B) and (C) , also comprises ~~comprising~~ at least one molecular unit ~~or consisting essentially of a molecular unit~~, said molecular unit having a triplet energy which is greater than that of the emission level of the complexed rare-earth metal ion.

31. (Currently Amended): The conjugate as claimed in claim 30, wherein the rare-earth metal cryptate consists of a rare-earth metal salt complexed with one of the macrocyclic or macropolycyclic compounds selected from the following compounds below:

2.2.phenanthroline, 2.2.phenanthroline amide, 2.2.anthracene, 2.2.anthracene amide, 2.2.biisoquinoline, 2.2.biphenyl-bis-pyridine, 2.2.bipyridine, 2.2.bipyridine amide, trisbipyridine, trisphenanthroline, phenanthrolinebisbipyridine, biisoquinolinebisbipyridine, bisbipyridine diphenylbipyridine, and macropolycyclic compounds comprising a molecular unit chosen from bipyrazines, bipyrimidines and nitrogen-containing heterocycles comprising N-oxide groups.

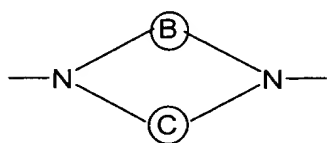
~~[2.2.phenanthroline]; [2.2.phenanthroline amide]; [2.2.anthracene]; [2.2.anthracene amide]; [2.2.biisoquinoline]; [2.2.biphenyl-bis-pyridine]; [2.2.bipyridine]; [2.2.bipyridine amide]; the macropolycycles trisbipyridine, trisphenanthroline, phenanthrolinebisbipyridine, biisoquinolinebisbipyridine, bisbipyridine diphenylbipyridine; a macropolycyclic compound comprising a molecular unit chosen from bipyrazines, bipyrimidines and nitrogen-containing heterocycles comprising N-oxide groups.~~

32. (Currently Amended): The conjugate as claimed in claim 20, wherein the rare-earth metal cryptate consists of at least one rare-earth metal salt complexed with a macropolycyclic compound corresponding to one of the formulae II or III below:

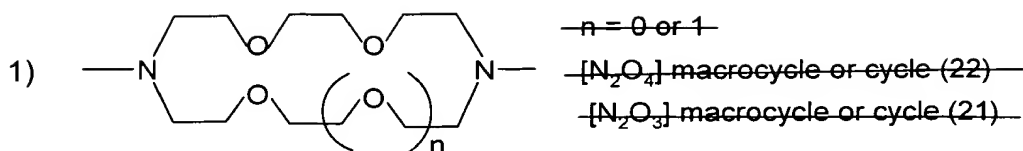


in which:

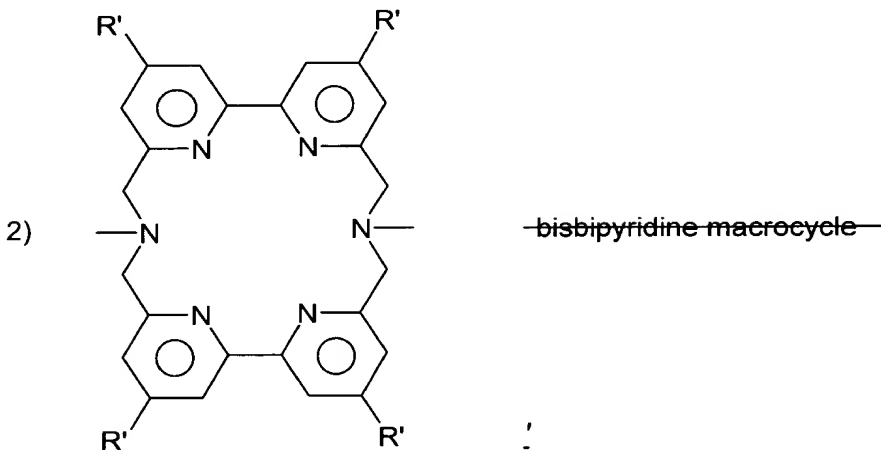
- the ring of formula



is one of the following rings:



wherein n is 0 or 1,



[[(-)]Y is a spacer group or spacer arm which ~~is consists of~~ a divalent organic radical [[(,)] chosen from;

linear or branched C_1 or C_{20} alkylene ~~groups~~ optionally containing one or more double bonds and/or optionally containing one or more hetero atoms ~~such as oxygen, nitrogen, sulfur or phosphorus~~ or one or more carbamoyl or carboxamido group(s), [[(,)] ~~chosen from~~

C_5 to C_8 cycloalkylene, and groups or chosen from

C_6 to C_{14} arylene ~~groups,~~

said alkylene, cycloalkylene or arylene are in each case ~~groups being~~ optionally substituted with alkyl, aryl or sulfonate groups;

[[(-)] Z is a functional group capable of bonding covalently to a biological substance;

[[(-)] R is a methyl ~~group or represents the group~~ -Y-Z;

[[(-)] R' is hydrogen, ~~or a group~~ -COOR'', or -CO-NH-Y-Z; in which

R'' is a C₁ to C₁₀ alkyl group or alternatively R' is a group ~~CO-NH-Y-Z~~.

33. (Currently Amended): The conjugate as claimed in claim 20, wherein the rare-earth metal cryptate is bonded to the oligonucleotide via a spacer arm, wherein said spacer arm is consisting of a divalent organic radical chosen from:

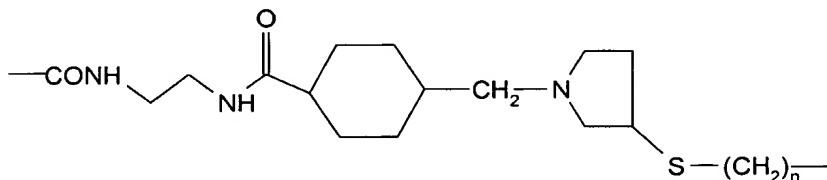
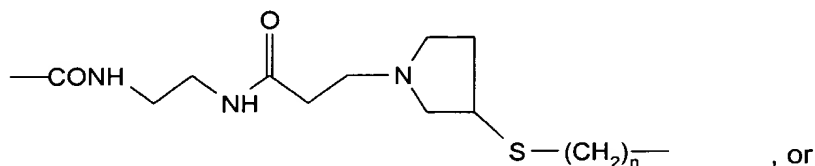
C₁-C₂₀ linear or branched alkylene ~~groups~~ optionally containing one or more double bonds or triple bonds and/or optionally containing one or more hetero atoms, ~~such as oxygen, nitrogen, sulfur, phosphorus~~ or one or more carbamoyl or carboxamino group(s);

C₅-C₈ cycloalkylene; ~~groups~~ and

C₆-C₁₄ arylene ~~groups~~; [[,]]

wherein said alkylene, cycloalkylene or arylene is in each case ~~groups being~~ optionally substituted with alkyl, aryl or sulfonate groups.

34. (Currently Amended): The conjugate as claimed in claim 33, wherein the spacer arm is:



wherein n is [[=]] 2 to 6; [[,]] or

the spacer arm is -CONH-(CH₂)_{6-i}; [[,]]

wherein the attachment to the cryptate is via the group -CONH ~~taking place on the cryptate~~.

35. (Previously Presented): The conjugate as claimed in claim 20, wherein the rare-earth metal cryptate is a europium cryptate.

36. (Previously Presented): The conjugate as claimed in claim 35, wherein ~~the rare-earth metal cryptate is the~~ said europium cryptate is Eu trisbipyridine or Eu [bisdiethoxybipyridine.bipyridine].

37. (Previously Presented): The conjugate as claimed in claim 21, wherein the biological molecule is a cellular receptor, an antigen, an antibody or a nucleic acid.

38. (Previously Presented): The conjugate as claimed in claim 32, wherein the R" alkyl group is a methyl, ethyl or tert-butyl group.

39. (Currently Amended): The conjugate as claimed in claim 33, wherein said one or more hetero atoms ~~the at least one hetero atom~~ is oxygen, nitrogen, sulfur, or phosphorus.

40. (Previously Presented): The process according to claim 12, wherein R" is a methyl, an ethyl or a tert-butyl group.

41. (Canceled)

42. (Canceled)

43. (Canceled)

44. (Canceled)

45. (Canceled)

46. (Canceled)

47. (New): The process according to claim 1, wherein said rare-earth metal cryptate is bonded to said oligonucleotide via a spacer arm, where in said spacer arm is a divalent organic radical chosen from:

a C₁-C₂₀ linear or branched alkylene optionally containing one or more double bonds or triple bonds and/or optionally containing one or more hetero atoms selected from oxygen, nitrogen, sulfur, and phosphorus or one or more carbamoyl or carboxamino group(s);

a C₅-C₈ cycloalkylene; and

C₆-C₁₄ arylene,

wherein in each case said alkylene, cycloalkylene or arylene is optionally substituted by alkyl, aryl or sulfonate groups.

48. (New): The process as claimed in claim 3, wherein the oligonucleotide consists of a chain of ribonucleotide or deoxyribonucleotide units bonded to one another via natural phosphodiester internucleotide bonds, wherein some of the internucleotide bonds are replaced with phosphonate, phosphoramidate or phosphorothioate bonds.

49. (New): The process as claimed in claim 9, wherein said rare-earth metal cryptate is directly bonded covalently to the oligonucleotide.

50. (New): The process as claimed in claim 9, wherein the rare-earth metal cryptate is bonded covalently to the oligonucleotide via a spacer arm.

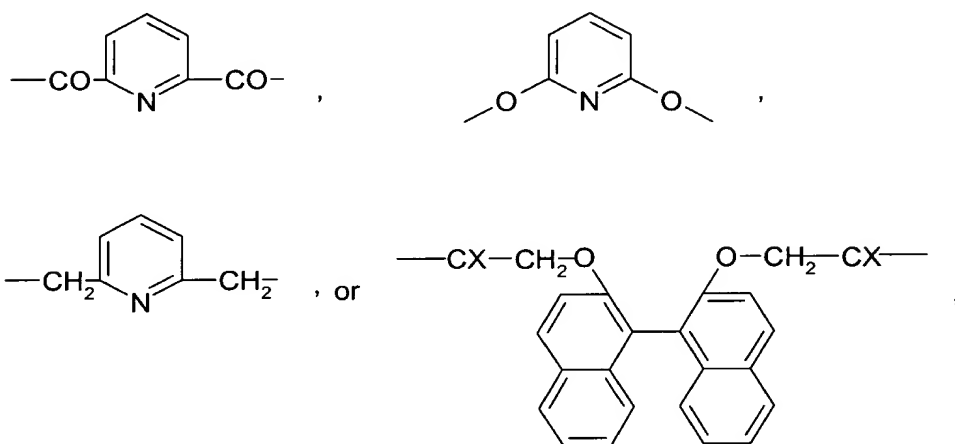
51. (New): The process as claimed in claim 10, wherein at least one of the radicals (A) , (B) and (C) , consists essentially of a molecular unit having a triplet energy which is greater than that of the emission level of the complexed rare-earth metal ion.

52. (New): The process according to claim 10, wherein

said molecular unit is phenanthroline, anthracene, benzene, naphthalene, biphenyl, terphenyl, azobenzene, azopyridine, pyridine, bipyridine, bisquinoline, $-\text{C}_2\text{H}_4-\text{X}_1-\text{C}_6\text{H}_4-\text{X}_2-\text{C}_2\text{H}_4-$, or $\text{C}_2\text{H}_4-\text{X}_1-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-\text{X}_2-\text{C}_2\text{H}_4-$, and

X_1 and X_2 are each O, N, or S, or

said molecular unit is



and X is oxygen or hydrogens.

53. (New): The conjugate according to claim 20, wherein said rare-earth metal cryptate is bonded to said oligonucleotide via a spacer arm, where in said spacer arm is a divalent organic radical chosen from:

a C_1-C_{20} linear or branched alkylene optionally containing one or more double bonds or triple bonds and/or optionally containing one or more hetero atoms selected from oxygen, nitrogen, sulfur, and phosphorus or one or more carbamoyl or carboxamino group(s);

a C_5-C_8 cycloalkylene; and

C_6-C_{14} arylene,

wherein in each case said alkylene, cycloalkylene or arylene is optionally substituted by alkyl, aryl or sulfonate groups.

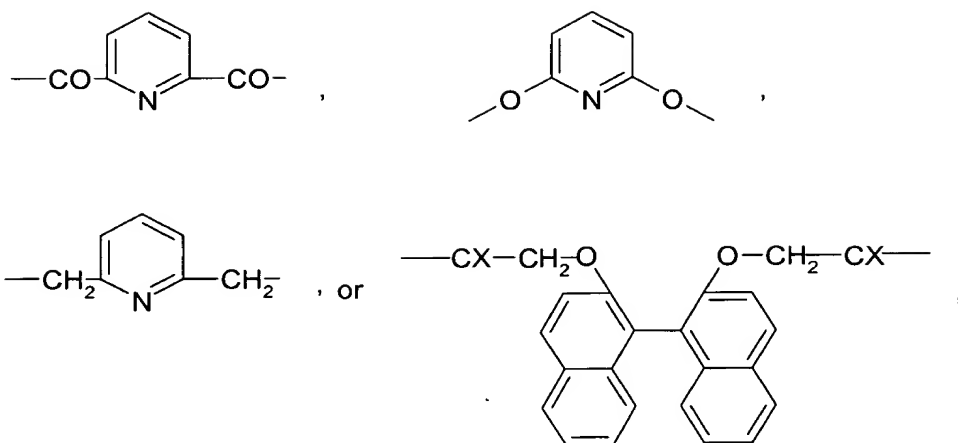
54. (New): The conjugate as claimed in claim 23, wherein the oligonucleotide consists of a chain of ribonucleotide or deoxyribonucleotide units bonded to one another via natural phosphodiester internucleotide bonds, wherein some of the internucleotide bonds are replaced with phosphonate, phosphoramidate or phosphorothioate bonds.

55. (New): The conjugate as claimed in claim 29, wherein said rare-earth metal cryptate is directly bonded covalently to the oligonucleotide.

56. (New): The conjugate as claimed in claim 29, wherein the rare-earth metal cryptate is bonded covalently to the oligonucleotide via a spacer arm.

57. (New): The conjugate as claimed in claim 30, wherein at least one of the radicals (A) , (B) and (C) , consists essentially of a molecular unit having a triplet energy which is greater than that of the emission level of the complexed rare-earth metal ion.

58. (New): The conjugate according to claim 30, wherein
said molecular unit is phenanthroline, anthracene, benzene, naphthalene, biphenyl, terphenyl, azobenzene, azopyridine, pyridine, bipyridine, bisquinoline, -C₂H₄-X₁-C₆H₄-X₂-C₂H₄-, or C₂H₄- X₁-CH₂-C₆H₄-CH₂-X₂-C₂H₄-, and
X₁ and X₂ are each O, N, or S, or
said molecular unit is



and X is oxygen or hydrogen.

59. (New): The process according to claim 1, wherein the oligonucleotide is an oligodeoxynucleotide modified at its 5' end with an aminohexyl group for binding to said cryptate, and modified at 3' end with a structure containing a maleimide group for binding to the biological molecule.

60. (New): The conjugate according to claim 20, wherein the oligonucleotide is an oligodeoxynucleotide modified at its 5' end with an aminohexyl group for binding to said cryptate, and modified at 3' end with a structure containing a maleimide group for binding to the biological molecule.

61. (New): The process according to claim 1, wherein the oligonucleotide is a thiol-oligonucleotide wherein the thiol function is introduced at the 5' end of the oligonucleotide in the form of a disulfide bond.

62. (New): The conjugate according to claim 20, wherein the oligonucleotide is a thiol-oligonucleotide wherein the thiol function is introduced at the 5' end of the oligonucleotide in the form of a disulfide bond.